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A Study of AK104 (an Anti-PD1 and Anti-CTLA4 Bispecific Antibody) combined with standard therapy for the first-line treatment of recurrent or metastatic cervical cancer(R/M CC)

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Background

- Platinum-based chemotherapy+/-bevacizumab has been widely used as standard first-line treatment for R/M CC. [1]
- Pembrolizumab plus chemotherapy+/-bevacizumabIn was newly approved by FDA to treat R/M CC patients with CPS ≥1(Keynote 826, ORR: 68% and PFS: 10.4 months in pembrolizumab group).[2]
- AK104 is a bispecific antibody targeting PD1 and CTLA4. AK104 monotherapy has shown promising efficacy and tolerable toxicity in pre-treated R/M CC, with ORR of 33.0% and mPFS of 3.75 months(NCT04380805).[3]
- In this study, we reported the efficacy and safety of AK104 in combination with platinum-based chemotherapy+/-bevacizumab for the first line treatment of R/M CC (NCT04868708).

1. NCCN guideline 2021.
2. Colombo N, et al. N Engl J Med. 2021 Nov 11;385(20):1856-1867.
3. Xiaohua Wu, et al. SGO 2022 oral presentation.

AK104-210 Study Design

A Multi-center, Open-label, Phase II study to evaluate safety and efficacy of AK104 in combination with platinum-based chemotherapy+/-bevacizumab in first-line treatment of R/M cervical cancer.

Key Eligibility Criteria:

- Recurrent or metastatic cervical cancer not amenable to curative treatment
- Histology types include：quamous cell carcinoma, adenocarcinoma, or adenosquamous cell carcinoma
- No prior systemic chemotherapy
- ECOG PS 0-1

N=45

Cohort A-15 (n=15):
AK104 15mg/kg IV Q3W +
Paclitaxel + Cisplatin or Carboplatin IV Q3W[a]

Cohort A-10 (n=15):
AK104 10mg/kg IV Q3W +
Paclitaxel + Cisplatin or Carboplatin IV Q3W[a]

Cohort B-10 (n=15):
AK104 10mg/kg IV Q3W +
Paclitaxel + Cisplatin or Carboplatin IV Q3W[a]
+ Bevacizumab 15 mg/kg IV Q3W

Treatment until:

- Disease progression
- Unacceptable toxicity
- Withdrawal of consent

End Points:

- Primary end point: safety
- Secondary end points: ORR, DOR, DCR, PFS per RECIST1.1 by investigator and OS, PK/PD, ADA, etc.

[a]Paclitaxel: 175 mg/m2, Cisplatin: 50 mg/m2, Carboplatin: AUC 5 mg/mL/min.
ClinicalTrials.gov, NCT04868708.

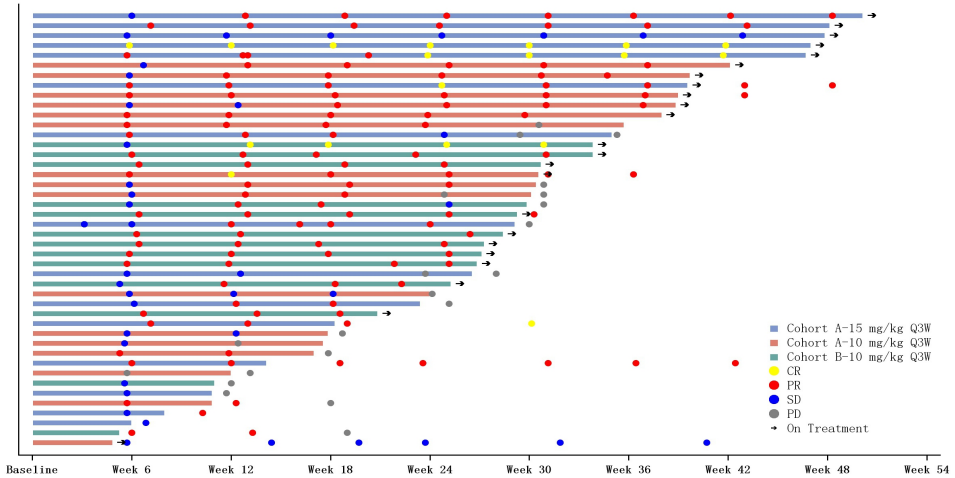
Baseline characteristics

	Total (N=45)	A-15 (N=15)	A-10 (N=16)	B-10 (N=14)
Age, median (range)	52.4 (33, 71)	52.4 (35, 67)	55.9 (39, 69)	50.8 (33, 71)
ECOG PS 1, n (%)	26 (57.8)	10 (66.7)	12 (75.0)	4 (28.6)
Squamous cell carcinoma, n (%)	39 (86.7)	11 (73.3)	15 (93.8)	13 (92.9)
Stage at initial diagnosis (FIGO 2018), n (%)				
I	11 (24.4)	4 (26.7)	5 (31.3)	2 (14.3)
II	8 (17.8)	5 (33.3)	2 (12.5)	1 (7.1)
IIIB	4 (8.9)	1 (6.7)	3 (18.8)	0
IIIC	14 (31.1)	4 (26.7)	3 (18.8)	7 (50.0)
IVA	1 (2.2)	0	1 (6.3)	0
IVB	7 (15.6)	1 (6.7)	2 (12.5)	4 (28.6)
Disease status, n (%)				
Recurrent without distant metastases	12 (26.7)	4 (26.7)	5 (31.3)	3 (21.4)
Metastatic	33 (73.3)	11 (73.3)	11 (68.8)	11 (78.6)
PD-L1 CPS, n (%)				
<1	17 (37.8)	5 (33.3)	8 (50.0)	4 (28.6)
1 to <10	15 (33.3)	5 (33.3)	4 (25.0)	6 (42.9)
≥10	13 (28.9)	5 (33.3)	4 (25.0)	4 (28.6)
Prior therapy, n (%)				
Surgery only	5 (11.1)	2 (13.3)	2 (12.5)	1 (7.1)
Chemoradiation or radiation only	19 (42.2)	5 (33.3)	8 (50.0)	6 (42.9)
Chemoradiation or radiation with surgery	14 (31.1)	7 (46.7)	4 (25.0)	3 (21.4)
None	7 (15.6)	1 (6.7)	2 (12.5)	4 (28.6)

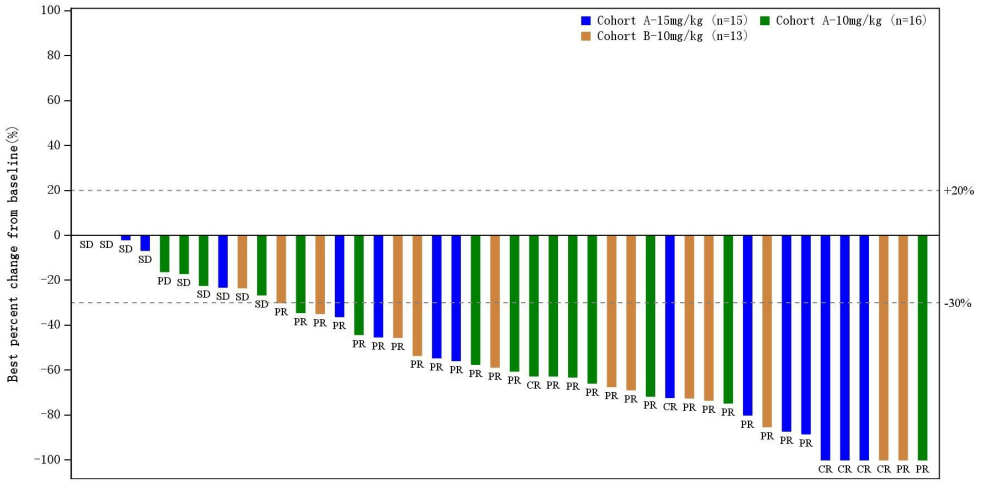
Data cutoff date: Apr 18, 2022

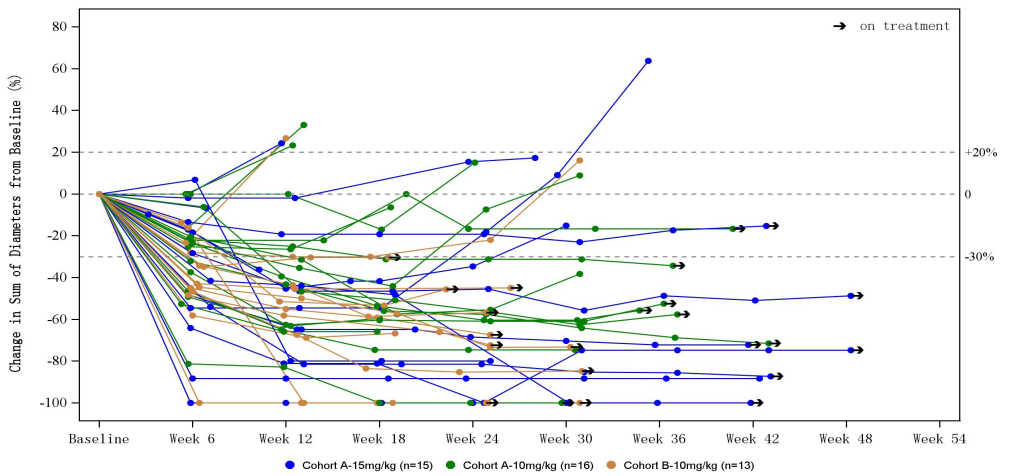
Efficacy

Confirmed ORR was 66.7%, 68.8% and 92.3% in A-15, A-10 and B-10, respectively(Per RECIST1.1).



	A-15 (N=15)	A-10 (N=16)	B-10 (N=13)[a]	A-10+B-10 (N=29)
Objective Response Rate, n(%)	**10 (66.7)**	**11 (68.8)**	**12 (92.3)**	**23 (79.3)**
Disease Control Rate, n (%)	**15 (100.0)**	**15 (93.8)**	**13 (100.0)**	**28 (96.6)**
Best Overall Response, n(%)				
Complete Response	**2 (13.3)**	**0 (0.0)**	**1 (7.7)**	**1 (3.4)**
Partial Response	**8 (53.3)**	**11 (68.8)**	**11 (84.6)**	**22 (75.9)**
Stable Disease	5 (33.3)	4 (25.0)	1 (7.7)	5 (17.2)
Progressive Disease	0	1 (6.3)	0	1 (3.4)
Median DoR, [95%CI], months	NR (2.99, NE)	5.75 (2.86, NE)	NR (3.02, NE)	NR (4.27, NE)
Median TTR, (range), months	1.51(1.31,2.96)	1.35(1.22,4.24)	1.48(1.31,3.02)	1.48(1.22,4.24)





Data cutoff date: 18 Apr 2022.
[a]One patient died before first tumor assessment.

Efficacy

Benefit was favorable regardless of CPS status.

	A-15		A-10		B-10		A-10+B-10	
	CPS≥1 (N=10)	CPS<1 (N=5)	CPS≥1 (N=8)	CPS<1 (N=8)	CPS≥1 (N=9)	CPS<1 (N=4)	CPS≥1 (N=17)	CPS<1 (N=12)
Objective Response Rate, n(%)	**7 (70.0)**	**3 (60.0)**	**6 (75.0)**	**5 (62.5)**	**8 (88.9)**	**4 (100.0)**	**14 (82.4)**	**9 (75.0)**
Disease Control Rate, n (%)	**10 (100.0)**	**5 (100.0)**	**8 (100.0)**	**7 (87.5)**	**9 (100.0)**	**4 (100.0)**	**17 (100.0)**	**11 (91.7)**
Best Overall Response, n(%)								
Complete Response	2 (20.0)	0	0 (0.0)	0	1 (11.1)	0	1 (5.9)	0
Partial Response	5 (50.0)	3 (60.0)	6 (75.0)	5 (62.5)	7 (77.8)	4 (100.0)	13 (76.5)	9 (75.0)
Stable Disease	3 (30.0)	2 (40.0)	2 (25.0)	2 (25.0)	1 (11.1)	0	3 (17.6)	2 (16.7)
Progressive Disease	0	0	0	1 (12.5)	0	0	0	1 (8.3)

Data cutoff date: 18 Apr 2022.

Safety Overview

	Total (N=45)	A-15 (N=15)	A-10 (N=16)	B-10 (N=14)
TRAE, n (%)	45 (100.0)	15 (100.0)	16 (100.0)	14 (100.0)
Grade ≥3 TRAE, n (%)	27 (60.0)	9 (60.0)	7 (43.8)	11 (78.6)
TRSAE, n (%)	20 (44.4)	7 (46.7)	4 (25.0)	9 (64.3)
AK104 related TRSAE, n (%)	17 (37.8)	7 (46.7)	4 (25.0)	6 (42.9)
irAE, n (%)	25 (55.6)	10 (66.7)	8 (50.0)	7 (50.0)
Grade ≥3 irAE, n (%)	7 (15.6)	4 (26.7)	1 (6.3)	2 (14.3)
TRAE leading to treatment discontinuation, n (%)	6 (13.3)	3 (20.0)	0	3 (21.4)
TRAE leading to death, n (%)	1 (2.2)[a]	0	0	1 (7.1)

Data cutoff date: 18 Apr 2022.
[a]One death due to hemorrhagic shock occured in cohort B-10 and was judged as Bevacizumab-related.

TRAE

Related to any treatment, Incidence ≥20%

PT Term, n (%)	Total (N=45)		A-15 (N=15)		A-10 (N=16)		B-10 (N=14)	
	All Grade	Grade 3-4	All Grade	Grade 3-4	All Grade	Grade 3-4	All Grade	Grade 3-4
Subjects with at least one TRAE	**45 (100.0)**	**27 (60.0)**	**15 (100.0)**	**9 (60.0)**	**16 (100.0)**	**7 (43.8)**	**14 (100.0)**	**11 (78.6)**
Anaemia	**30 (66.7)**	**9 (20.0)**	11 (73.3)	**5 (33.3)**	10 (62.5)	**2 (12.5)**	9 (64.3)	**2 (14.3)**
White blood cell count decreased	**26 (57.8)**	**5 (11.1)**	10 (66.7)	0	10 (62.5)	**3 (18.8)**	6 (42.9)	**2 (14.3)**
Neutrophil count decreased	**13 (28.9)**	**6 (13.3)**	4 (26.7)	1 (6.7)	5 (31.3)	**2 (12.5)**	4 (28.6)	**3 (21.4)**
Hypoaesthesia	**13 (28.9)**	0	3 (20.0)	0	5 (31.3)	0	5 (35.7)	0
Decreased appetite	**12 (26.7)**	0	4 (26.7)	0	4 (25.0)	0	4 (28.6)	0
Rash	**12 (26.7)**	2 (4.4)	4 (26.7)	1 (6.7)	4 (25.0)	1 (6.3)	4 (28.6)	0
Vomiting	**11 (24.4)**	0	2 (13.3)	0	5 (31.3)	0	4 (28.6)	0
Platelet count decreased	**10 (22.2)**	**5 (11.1)**	4 (26.7)	**3 (20.0)**	2 (12.5)	1 (6.3)	4 (28.6)	1 (7.1)
Hepatic function abnormal	**10 (22.2)**	1 (2.2)	4 (26.7)	1 (6.7)	2 (12.5)	0	4 (28.6)	0
Pain in extremity	**9 (20.0)**	0	3 (20.0)	0	5 (31.3)	0	1 (7.1)	0

Data cutoff date: 18 Apr 2022.

irAE

Incidence ≥2 subjects

PT Term, n (%)	Total (N=45)		A-15 (N=15)		A-10 (N=16)		B-10 (N=14)	
	All Grade	Grade 3-4	All Grade	Grade 3-4	All Grade	Grade 3-4	All Grade	Grade 3-4
Subjects with at least one irAE	25(55.6)	7 (15.6)	10 (66.7)	4 (26.7)	8 (50.0)	1 (6.3)	7 (50.0)	2 (14.3)
Alanine aminotransferase increased	5 (11.1)	0	4 (26.7)	0	1 (6.3)	0	0	0
Rash	5 (11.1)	2 (4.4)	2 (13.3)	1 (6.7)	2 (12.5)	1 (6.3)	1 (7.1)	0
Hypothyroidism	5 (11.1)	0	1 (6.7)	0	3 (18.8)	0	1 (7.1)	0
Hyperthyroidism	4 (8.9)	0	1 (6.7)	0	2 (12.5)	0	1 (7.1)	0
Infusion related reaction	4 (8.9)	0	2 (13.3)	0	1 (6.3)	0	1 (7.1)	0
Aspartate aminotransferase increased	3 (6.7)	0	2 (13.3)	0	1 (6.3)	0	0	0
Hepatic function abnormal	3 (6.7)	0	2 (13.3)	0	1 (6.3)	0	0	0
Amylase increased	2 (4.4)	0	0	0	0	0	2 (14.3)	0

Data cutoff date: 18 Apr 2022.

Conclusion

- No new safety signals were observed in our study. AK104 in combination with platinum-based chemotherapy+/-bevacizumab was well tolerated.
- AK104 in combination with platinum-based chemotherapy+/-bevacizumab showed promising antitumor activity, regardless of CPS status.
  - ORR were 66.7%, 68.8% and 92.3% in A-15, A-10 and B-10, respectively
  - DCR were 100%, 93.8% and 100% in A-15, A-10 and B-10, respectively
- PFS or OS data is not mature by cut-off date.
- A phase III trial is ongoing to evaluate the efficacy and safety of AK104 plus platinum-based chemotherapy+/-bevacizumab in first-line treatment for R/M cervical cancer(NCT04982237).